CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206610Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Shetarra Walker, MD, MSCR Acting Team Leader
Division of Pediatric and Maternal Health

John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 206-610

Sponsor: Mylan

Drug: Acetaminophen for Injection

Dosage form and route of administration: powder, intravenous infusion

Proposed Indications:

- Management of mild to moderate pain in adult and pediatric patients 2 years and older
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older
- Reduction of fever in adult and pediatric patients

Consult request: The Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) requests DPMH's assistance with the review of the revised labeling for Acetaminophen for Injection since pediatric exclusivity has expired.

Background
In January 2020, DPMH was consulted to provide labeling recommendations for a 505(b)(2) application for Acetaminophen for Injection (NDA 206-610). At that time, the reference product, Ofirmev® (NDA 22-450), was under exclusivity for "revisions to the package insert based on data from a randomized placebo controlled, multicenter study of intravenous acetaminophen for the treatment of acute pain in pediatric patients to fulfill the postmarketing-requirement 1704-1." Although the study failed to demonstrate effectiveness for acute pain in pediatric patients from birth to less than 2 years, there was sufficient safety and pharmacokinetic data to permit extrapolation of efficacy for reduction of fever in pediatric patients less than 2 years. The pediatric exclusivity expired on July 27, 2020. DAAP requested DPMH's input on revising the proposed labeling to add information previously under pediatric exclusivity.

The formulation of Acetaminophen for Injection differs from the reference product Ofirmev® in that it is a lyophilized powder intended for intravenous infusion after reconstitution. Ofirmev® is a solution.

Pediatric Research Equity Act (PREA)
This 505(b)(2) Acetaminophen for Injection represents a new dosage form and, therefore, triggers PREA.

Reviewer comment: This product is relying on the findings of safety and efficacy of Ofirmev®. No additional studies under PREA are needed if the Applicant's product is adequately labeled for pediatric use.

DPMH Labeling Recommendations
The DPMH labeling recommendations are as follows. Recommended information to be added to selected sections of labeling is underlined. Information to be deleted has a strikethrough.

Highlights
Indications and Usage
Acetaminophen for injection is indicated for the

- Management of mild to moderate pain in adult and pediatric patients 2 years and older (1)
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older (1)
- Reduction of fever in adult and pediatric patients ~~2 years and older~~ (1)

Reviewer comment: The qualifier "2 years and older" is no longer needed since information related to patients less than 2 years can be added to labeling.

Dosage and Administration

- Acetaminophen for injection may be given as a single or repeated dose. (2.1)
- Acetaminophen for injection should be administered only as a 15-minute intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:

- 1,000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4,000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:

- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:

- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

Neonates and Infants:

- Neonates including premature neonates born at ≥ 32 weeks gestational age to 28 days chronological age, 12.5 mg/kg every 6 hours to a maximum of 50 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)
- Infants (29 days to 2 years of age): 15 mg/kg every 6 hours to a maximum of 60 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)

Reviewer comment: The information related to neonates and infants can be added back.

Use in Specific Populations

- Pediatric Use: The effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established. The safety and effectiveness of acetaminophen for injection in pediatric patients is supported by evidence from adequate and well controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)
- Hepatic Impairment: Acetaminophen for injection is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)
- Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

(b) (4)

Reviewer comment: The statement under Pediatric Use in the Highlights Section is the same as the one in the Ofirmev® labeling. However, providing information about the support for safety and effectiveness is not necessary in the Highlights Section. This information is in subsection 8.4 as it should be. DAAP should consider removing the second sentence under Pediatric Use above in the Ofirmev® labeling as well as this product's labeling.

The disclaimer is no longer needed.

Full Prescribing Information

1 Indications and Usage

Acetaminophen for injection is indicated for

- the management of mild to moderate pain in adult and pediatric patients 2 years and older
- the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older
- the reduction of fever in adult and pediatric patients ~~2 years and older~~.

Reviewer comment: The qualifier "2 years and older" is no longer needed.

2 Dosage and Administration

2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of acetaminophen for injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of acetaminophen for injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

Table 2. Dosing for Children

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3,750 mg)

(b) (4)

Reviewer comment: The disclaimer at the end of subsection 2.3 is no longer needed since subsection 2.4 will be added to the labeling.

2.4 Recommended Dosage for Treatment of Fever in Neonates and Infants

Neonates, including premature neonates born at ≥ 32 weeks gestational age, up to 28 days chronological age: the recommended dosage of acetaminophen for injection is 12.5 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 50 mg/kg per day, with a minimum dosing interval of 6 hours.

Infants 29 days to 2 years of age: the recommended dosage of acetaminophen for injection is 15 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 60 mg/kg per day, with a minimum dosing interval of 6 hours.

Table 3. Dosing for Treatment of Fever in Neonates and Infants

Age group	Dose given every 6 hours	Maximum total daily dose of acetaminophen (by all routes)
Neonates (birth to 28 days)	12.5 mg/kg	50 mg/kg
Infants (29 days to 2 years)	15 mg/kg	60 mg/kg

Reviewer comment: Subsection 2.4 should be added to labeling.

6 Adverse Reactions
6.1 Clinical Trial Experience
Pediatric Population

A total of 483~~355~~ pediatric patients (724~~7~~ neonates, 167~~64~~ infants, 171 children, and 73 adolescents) have received acetaminophen for injection in active-controlled (n=250) and open-label clinical trials (n=225), including 43.9~~59.7~~% (n=212) who received 5 or more doses and 31.2~~43.1~~% (n=153) who received more than 10 doses. Pediatric patients received acetaminophen for injection doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with acetaminophen for injection were nausea, vomiting, constipation, and pruritus.

Other Adverse Reactions Observed During Clinical Studies of Acetaminophen for Injection in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with acetaminophen for injection (n=483~~355~~) that occurred with an incidence of at least 1%.

~~Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection product. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that pediatric information.~~

Reviewer comment: The number of patients should be revised to add the neonates and infants studied in the clinical trial supporting protected pediatric information. The disclaimer is no longer needed at the end of subsection 6.1.

8 Use in Specific Population
8.4 Pediatric Use
Treatment of Acute Pain

The safety and effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of acetaminophen for injection in adults and safety and pharmacokinetic data from adult and ~~483~~355 pediatric patients across all age groups *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

The effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.

In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.

Treatment of Fever

The safety and effectiveness of acetaminophen for injection for the treatment of fever in pediatric patients, including premature neonates born at ≥ 32 weeks gestational age is supported by adequate and well-controlled studies of acetaminophen for injection in adults, ~~and~~ clinical studies in 244 pediatric patients 2 years and older, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age.

> ~~Additional information describing a clinical study in which safety and efficacy was not demonstrated in pediatric patients is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this product is not labeled with that pediatric information.~~

Reviewer comment: The information related to pediatric patients less than 2 years should be added to labeling. The disclaimer at the end of subsection 8.4 is no longer needed.

12 Clinical Pharmacology
12.3 Pharmacokinetics

Distribution

The pharmacokinetics of acetaminophen for injection have been studied in patients and healthy subjects up to 60 years old. The pharmacokinetic profile of acetaminophen for injection has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1,000 mg.

The maximum concentration (C_{max}) occurs at the end of the 15-minute intravenous infusion of acetaminophen for injection. Compared to the same dose of oral acetaminophen, the C_{max} following administration of acetaminophen for injection is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

Pharmacokinetic parameters of acetaminophen for injection (AUC, C_{max}, terminal elimination half-life [$T_{½}$], systemic clearance [CL], and volume of distribution at steady

state [V_{ss}]) following administration of a single intravenous dose of 15 mg/kg in children and adolescents and 1000 mg in adults are summarized in Table 5.

Table 5. Acetaminophen for Injection Pharmacokinetic Parameters

Subpopulations	Mean (SD)				
	AUC_{0-6h} (µg × h/mL)	C_{max} (µg/mL)	$T_{½}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)
Children	38 (8)	29 (7)	3.0 (1.5)	0.34 (0.10)	1.2 (0.3)
Adolescents	41 (7)	31 (9)	2.9 (0.7)	0.29 (0.08)	1.1 (0.3)
Adults	43 (11)	28 (21)	2.4 (0.6)	0.27 (0.08)	0.8 (0.2)

The concentrations of acetaminophen observed in neonates greater than 32 weeks gestational age at birth treated with 12.5 mg/kg dose are similar to infants, children and adolescents treated with a 15 mg/kg dose, and similar to adults treated with a 1,000 mg dose.

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

~~Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that information~~

Reviewer comment: The information related to neonates should be added to labeling. The disclaimer at the end of subsection 12.3 is no longer needed.

14 Clinical Studies

14.3 Pediatric Acute Pain and Fever

Acetaminophen for injection was studied in pediatric patients in three (b) (4) -active-controlled trials and three open-label safety and pharmacokinetic trials *[see Use in Specific Populations (8.4)]*.

~~Additional information describing clinical studies in which safety and efficacy were not demonstrated in pediatric patients is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this product is not labeled with that pediatric information.~~

Reviewer comment: The number of active-controlled trials can be revised to reflect all of the trials conducted. The disclaimer at the end of subsection 14.3 is no longer needed.

Additional Comment

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter for final approved labeling).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY M TAYLOR
09/23/2020 08:50:45 AM

SHETARRA E WALKER
09/23/2020 11:18:29 AM

JOHN J ALEXANDER
09/23/2020 11:31:53 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 17, 2020

To: Joshua Lloyd, M.D.
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Matthew W. Sullivan, M.S., RAC
Chief Project Management Staff, DAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ACETAMINOPHEN for injection for intravenous infusion

NDA: NDA 206610

In response to DAAP consult request dated January 17, 2020, OPDP has reviewed the proposed prescribing information (PI) and carton and container labeling for the original NDA submission for ACETAMINOPHEN for injection for intravenous infusion.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAP on January 16, 2020 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 13, 2019 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or koung.lee@fda.hhs.gov.

20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOUNG U LEE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
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Silver Spring, MD 20993
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MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 206-610

Sponsor: Mylan

Drug: Acetaminophen for Injection

Dosage form and route of administration: powder, intravenous infusion

Proposed Indications:

- Management of mild to moderate pain in adult and pediatric patients 2 years and older
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older
- Reduction of fever in adult and pediatric patients

Consult request: The Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) requests DPMH's assistance with the review of the proposed labeling for Acetaminophen for Injection as it relates to FDARA.

Background

The sponsor submitted NDA 206-610 for approval as a 505(b)(2) application. Their formulation of injectable acetaminophen differs from the reference product Ofirmev® (NDA 22-450) in that it is a lyophilized powder intended for intravenous infusion after reconstitution. Ofirmev® is a solution. The Orange Book reflects that Ofirmev® has exclusivity M-196*PED for "revisions to the package insert based on data from a randomized placebo controlled, multicenter study of intravenous acetaminophen for the treatment of acute pain in pediatric patients to fulfill the postmarketing-requirement 1704-1." Although the study failed to demonstrate effectiveness for acute pain in pediatric patients from birth to less than 2 years, there was sufficient safety and pharmacokinetic data to permit extrapolation of efficacy for reduction of fever in pediatric patients less than 2 years. The exclusivity will expire on July 27, 2020.

Pediatric Research Equity Act (PREA)

This 505(b)(2) Acetaminophen for Injection represents a new dosage form and, therefore, triggers PREA.

Reviewer comment: This product is relying on the findings of safety and efficacy of Ofirmev®. No additional studies under PREA are needed if the applicant is adequately labeled for pediatric use. Currently, some of the necessary pediatric information from Ofirmev® is protected by exclusivity. That information can be carved out of the proposed product's labeling without rendering the product less safe or effective for the remaining non-protected conditions of use and a disclaimer can be added to the labeling to reflect the carved out information. After expiration of pediatric exclusivity, the sponsor should add the carved out labeling language so that the product will be adequately labeled for pediatric use.

Federal Reauthorization Act of 2017 (FDARA)

505A(o)(l) & (2) state:

PROMPT APPROVAL OF DRUGS WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.—

"(1) GENERAL RULE.—A drug for which an application has been submitted or approved under subsection (b)(2) or (j) of section 505 shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent, or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(F), clause (iii) or (iv) of section 505(c)(3)(E), or section 527(a), or by an extension of such exclusivity under this section or section 505E."

"(2) LABELING.— Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(F), clauses (iii) and (iv) of section 505(c)(3)(E), or section 527, the Secretary may require that the labeling of a drug approved pursuant to an application submitted under subsection (b)(2) or (j) of section 505 that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include — ''(A) a statement that, because of marketing exclusivity for a manufacturer — ''(i) the drug is not labeled for pediatric use; or ''(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and ''(B)

a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use."

Reviewer comment: I recommend that a disclaimer be added to reflect the carved-out protected pediatric information. In this case, the protected information does not need to be retained for safe use of the product for remaining non-protected conditions of use.

DPMH Labeling Recommendations
The DPMH labeling recommendations are as follows (and align with the recommendations OGD made for generic versions of Ofirmev to date). Recommended information to be added to selected sections of labeling is underlined. Information to be deleted has a strikethrough.

Highlights
Indications and Usage
Acetaminophen for injection is indicated for the

- Management of mild to moderate pain in adult and pediatric patients 2 years and older (1)
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older (1)
- Reduction of fever in adult and pediatric patients 2 years and older (1)

Reviewer comment: OGD recommended the addition of the qualifier "2 years and older" during development of the labeling template for ANDA applications to clarify that "pediatric patients" does not include ages 0-2 years. I agree with this addition.

Dosage and Administration

- Acetaminophen for injection may be given as a single or repeated dose. (2.1)
- Acetaminophen for injection should be administered only as a 15-minute intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:

- 1,000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4,000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:

- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:

- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

~~**Neonates and Infants:**~~

- ~~Neonates including premature neonates born at ≥ 32 weeks gestational age to 28 days chronological age, 12.5 mg/kg every 6 hours to a maximum of 50 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)~~
- ~~Infants (29 days to 2 years of age): 15 mg/kg every 6 hours to a maximum of 60 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)~~

Use in Specific Populations

- ~~Pediatric Use: The effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established. The safety and effectiveness of acetaminophen for injection in pediatric patients is supported by evidence from adequate and well controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)~~
- Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)
- Hepatic Impairment: Acetaminophen for injection is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)
- Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

DPMH recommends that the following disclaimer should be added at the bottom of the Highlights section.

> Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection product. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Full Prescribing Information

1 Indications and Usage

Acetaminophen for injection is indicated for

- the management of mild to moderate pain in adult and pediatric patients 2 years and older
- the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older
- the reduction of fever in adult and pediatric patients 2 years and older.

Reviewer comment: See explanation for addition above.

2 Dosage and Administration

~~2.4 Recommended Dosage for Treatment of Fever in Neonates and Infants~~

~~Neonates, including premature neonates born at ≥ 32 weeks gestational age, up to 28 days chronological age: the recommended dosage of acetaminophen for injection is 12.5 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 50 mg/kg per day, with a minimum dosing interval of 6 hours.~~

~~Infants 29 days to 2 years of age: the recommended dosage of acetaminophen for injection is 15 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 60 mg/kg per day, with a minimum dosing interval of 6 hours.~~

~~Table 3. Dosing for Treatment of Fever in Neonates and Infants~~

~~Age group~~	~~Dose given every 6~~	~~Maximum total daily dose of~~

	~~hours~~	~~acetaminophen (by all routes)~~
~~N nat s (birth to 28 days)~~	~~12 5 mg/kg~~	~~50 mg/kg~~
~~Infants (29 days to 2 years)~~	~~15 mg/kg~~	~~60 mg/kg~~

DPMH recommends that, because the entire subsection 2.4 should be deleted, the following disclaimer should be added to the end of subsection 2.3.

> Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection product. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

6 Adverse Reactions
6.1 Clinical Trial Experience
Pediatric Population

A total of ~~483~~355 pediatric patients (~~72~~47 neonates, ~~167~~64 infants, 171 children, and 73 adolescents) have received acetaminophen for injection in active-controlled (n=250) and open-label clinical trials (n=225), including ~~43.9~~59.7% (n=212) who received 5 or more doses and ~~31.2~~43.1% (n=153) who received more than 10 doses. Pediatric patients received acetaminophen for injection doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with acetaminophen for injection were nausea, vomiting, constipation, and pruritus.

Other Adverse Reactions Observed During Clinical Studies of Acetaminophen for Injection in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with acetaminophen for injection (n=~~483~~355) that occurred with an incidence of at least 1%.

Reviewer comment: The number of patients should be revised to remove the neonates studied in the clinical trial supporting protected pediatric information.

DPMH recommends that the following disclaimer should be added to the end of subsection 6.1.

> Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection product. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8 Use in Specific Population
8.4 Pediatric Use
Treatment of Acute Pain

The safety and effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of acetaminophen for injection in adults and safety and

pharmacokinetic data from adult and ~~483~~355 pediatric patients across all age groups *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

~~The effectiveness of acetaminophen for injection for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.~~

~~In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.~~

Treatment of Fever

The safety and effectiveness of acetaminophen for injection for the treatment of fever in pediatric patients, ~~including premature neonates born at ≥ 32 weeks gestational age~~ is supported by adequate and well-controlled studies of acetaminophen for injection in adults, and clinical studies in 244 pediatric patients 2 years and older~~, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age~~.

Reviewer comment: The information related to pediatric patients less than 2 years should be deleted.

DPMH recommends that the following disclaimer should be added to the end of subsection 8.4.

> Additional information describing a clinical study in which safety and efficacy was not demonstrated in pediatric patients is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this product is not labeled with that pediatric information.

Reviewer comment: This disclaimer differs from recommended disclaimers in other subsections because of the need to explain that the clinical study did not demonstrate efficacy.

12 Clinical Pharmacology
12.3 Pharmacokinetics

Distribution

The pharmacokinetics of acetaminophen for injection have been studied in patients and healthy subjects up to 60 years old. The pharmacokinetic profile of acetaminophen for injection has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1,000 mg.

The maximum concentration (C_{max}) occurs at the end of the 15-minute intravenous infusion of acetaminophen for injection. Compared to the same dose of oral acetaminophen, the C_{max} following administration of acetaminophen for injection is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

Pharmacokinetic parameters of acetaminophen for injection (AUC, C_{max}, terminal elimination half-life [$T_{½}$], systemic clearance [CL], and volume of distribution at steady state [V_{ss}]) following administration of a single intravenous dose of 15 mg/kg in children and adolescents and 1000 mg in adults are summarized in Table 5.

Table 5. Acetaminophen for Injection Pharmacokinetic Parameters

Subpopulations	Mean (SD)				
	AUC_{0-6h} (µg × h/mL)	C_{max} (µg/mL)	$T_{½}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)
Children	38 (8)	29 (7)	3.0 (1.5)	0.34 (0.10)	1.2 (0.3)
Adolescents	41 (7)	31 (9)	2.9 (0.7)	0.29 (0.08)	1.1 (0.3)
Adults	43 (11)	28 (21)	2.4 (0.6)	0.27 (0.08)	0.8 (0.2)

~~The concentrations of acetaminophen observed in neonates greater than 32 weeks gestational age at birth treated with 12.5 mg/kg dose are similar to infants, children and adolescents treated with a 15 mg/kg dose, and similar to adults treated with a 1,000 mg dose.~~

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

Reviewer comment: The protected pediatric information related to neonates should be removed.

DPMH recommends that the following disclaimer should be added to the end of subsection 12.3.

> Additional pediatric use information is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this drug product is not labeled with that information

14 Clinical Studies

14.3 Pediatric Acute Pain ~~and Fever~~

Acetaminophen for injection was studied in pediatric patients in ~~three~~ <u>two</u> active-controlled trials and three open-label safety and pharmacokinetic trials *[see Use in Specific Populations (8.4)]*.

DPMH recommends that the following disclaimer should be added to the end of subsection 14.3.

> <u>Additional information describing clinical studies in which safety and efficacy</u>

were not demonstrated in pediatric patients is approved for Mallinckrodt IP's OFIRMEV (acetaminophen) Injection. However, due to Mallinckrodt IP's marketing exclusivity rights, this product is not labeled with that pediatric information.

Additional Comment

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter for final approved labeling).

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/s/

AMY M TAYLOR
01/02/2020 10:52:33 AM

JOHN J ALEXANDER
01/02/2020 02:41:35 PM
Signing for Dr. Hari Sachs

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 3, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 206610
Product Name and Strength:	Acetaminophen for Injection; 1,000 mg per vial
Applicant/Sponsor Name:	Mylan Pharmaceuticals Inc. (Mylan)
FDA Received Date:	May 2, 2019
OSE RCM #:	2018-2804-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

DAAAP requested that we review the revised container label and carton labeling for acetaminophen for injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling for acetaminophen for injection are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Acetaminophen (NDA 206610). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 13. RCM No.: 2018-2804.

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/s/

OTTO L TOWNSEND on behalf of CAMERON D JOHNSON
05/03/2019 09:57:00 AM

OTTO L TOWNSEND
05/03/2019 09:57:16 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 3, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 206610
Product Name and Strength:	Acetaminophen for Injection; 1,000 mg per vial
Applicant/Sponsor Name:	Mylan Pharmaceuticals Inc. (Mylan)
FDA Received Date:	May 2, 2019
OSE RCM #:	2018-2804-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

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2 CONCLUSION

The revised container label and carton labeling for acetaminophen for injection are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Acetaminophen (NDA 206610). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 13. RCM No.: 2018-2804.

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/s/

OTTO L TOWNSEND on behalf of CAMERON D JOHNSON
05/03/2019 09:57:00 AM

OTTO L TOWNSEND
05/03/2019 09:57:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 02-09-2015

From: Leyla Sahin, M.D.
Medical Officer,
Division of Pediatric and Maternal, Maternal Health Team

Through: Lynne P. Yao, M.D.
Acting Director,
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products

Drug: IV acetaminophen, NDA 206610

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Sponsor: Agila/Mylan

Materials Reviewed:
- Sponsor's proposed labeling
- Approved labeling for Ofirmev
- Literature review
- DPMH Ofirmev labeling review (2-9-2010)

Consult Question: Please assist in revising labeling in the PLLR format

BACKGROUND

Agila/Milan submitted a 505(b)(2) application On May 5, 2014, for injectable acetaminophen, for management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. The referenced innovator drug, Ofirmev®, was approved in 2010, and the Division of Pediatric and Maternal Health (DPMH), Maternal Health Team had provided labeling edits regarding the Pregnancy and Nursing Mothers subsections of labeling that included a review of the published literature (see review in DARRTS dated February 9, 2010). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted DPMH on January 8, 2015 to revise the Pregnancy and Nursing Mothers subsections of labeling to the format of the Pregnancy and Lactation Labeling Rule (PLLR), which published December 4, 2014. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable).[1] Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physician Labeling Rule (PLR)[2], to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format.

REVIEW OF PUBLISHED DATA

DAAAP recently published a Drug Safety Communication (DSC) regarding a possible association between *in utero* exposure to acetaminophen and attention deficit hyperactivity disorder (ADHD) in children that stated that the data are conflicting and inconclusive, and do not support labeling revisions at the present time.[3]

Since DPMH's review of the literature in 2010, there have not been any additional publications on the safety of acetaminophen in pregnancy or lactation, other than the published studies that were reviewed as part of the recent DSC.[4,5,6]

Since PLLR requires the inclusion of available information on serious known or potential risks to the pregnancy associated with the disease or condition for which the drug is indicated to be used, DPMH reviewed the literature regarding fever and pregnancy. A recent meta-analysis of 17 published case-control studies on the effect of fever in the first trimester of pregnancy showed a

---

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[2] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[3] http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm
[4] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014;168:313-20.
[5] Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. Teratology 1987;35:211-9.
[6] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol 2013;42:1702-13.

potential for increased risk of neural tube defects (OR 2.9 (95% CI 2.22-3.79)), oral clefts (OR 1.94 (95% CI 1.35-2.79)), and congenital heart defects (OR 1.54 (95% CI 1.37-1.74)).[7] Limitations of these studies included recall bias and fever diagnosis based on maternal report. In addition, few studies reported on the effect of duration or severity of the fever, or the underlying illness. A prospective cohort study of 115 pregnant who reported a fever of at least 38.9 degrees C lasting at least 24 hours (high fever group) compared with 147 women who reported a fever of either less than 38.9 degrees C or lasting less than 24 hours (low fever group) did not show a statistically significant increased risk of major birth defects.[8]

The Centers for Disease Control (CDC) website on influenza and pregnancy states the following: "Having a fever caused by flu infection or other infections early in pregnancy can lead to birth defects in an unborn child. Pregnant women who get a fever should treat their fever with Tylenol® (or store brand equivalent) and contact their doctor as soon as possible."[9] However the CDC website does not include a literature review or references of published studies that support the statement regarding an association between maternal fever and an increased risk for birth defects.

In light of conflicting findings and case control study results that are subject to recall bias and potential confounding from the underlying illness, DPMH does not recommend adding a statement to Clinical Considerations regarding an increased risk for birth defects due to fever.

LABELING RECOMMENDATIONS

DPMH revised labeling subsections 8.1, 8.2, and 8.3 for compliance with the PLLR (see Appendix A). DPMH refers to the final NDA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION
The purpose of Highlights is to highlight important information for the safe and effective use of a product. General information is not placed in this section, therefore for IV acetaminophen, there is no need to include any statement related to Pregnancy or Lactation. DPMH recommends deleting the sponsor's proposed language in this section.

8.1 Pregnancy

Risk Summary
The background rate in the general population should be added to the current statements.

Data
DPMH recommends adding information on the comparator groups.

[7] Dreier JW et al. 2014. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. Pediatrics. 133;e674-688.
[8] Chambers CD, et al. 1998. Maternal fever and birth outcome: a prospective study. Teratology. 58:251-257.
[9] http://www.cdc.gov/flu/protect/vaccine/pregnant.htm

8.2 Labor and Delivery

Under PLLR this subsection is renamed Labor or Delivery and is included under 8.1 Pregnancy, Clinical Considerations if the drug affects labor or delivery. DPMH recommends deleting the proposed language as there are no data to inform IV acetaminophen's effect on labor or delivery.

8.3 Nursing Mothers

Under PLLR this subsection is renamed "Lactation" and renumbered 8.2. DPMH recommends the inclusion of the Risk Summary and Data subheadings, the addition of the standard breastfeeding risk-benefit statement required by PLLR, and addition of details regarding the published lactation studies, such as clarification that the lactation studies were conducted in women exposed to oral acetaminophen.

APPENDIX A-DPMH Labeling Recommendations
IV Acetaminophen

8.1 Pregnancy

Risk Summary

There are no studies of intravenous acetaminophen in pregnant women. However, epidemiological data on oral acetaminophen use in pregnant women showed a similar rate of major birth defects compared to control groups of women with no prenatal exposure to acetaminophen. The background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Animal reproduction studies have not been conducted with IV acetaminophen; however, oral acetaminophen has been shown to be fetotoxic, embryotoxic, and has been shown to lead to reduced pup birth weights at 0.85, 1.2, and 0.43 times the clinical dose, respectively.

Data

Human Data

The results from a large Danish population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate a similar rate of major birth defects compared to a control group of unexposed children. The rate of major birth defects (4.3%) was similar to the rate in the general population in Denmark (4.28%). A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had a similar rate of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

Animal Data

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Lactation

Risk Summary

No lactation studies have been conducted with acetaminophen for injection; however, limited published lactation data report the presence of oral acetaminophen in human milk with a calculated infant daily dose of 1 to 2 % of the maternal dose. One published report describes a rash in a breastfed infant. No information is available regarding the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [Drug name] and any potential adverse effects on the breastfed infant from [Drug name] or from the underlying maternal condition.

Data

Data are available in 15 nursing mothers who took a single dose of 650-1000 mg oral acetaminophen between 2 to 22 months post-partum. The calculated infant daily dose of acetaminophen is approximately 1 to 2% of the maternal dose. No adverse reactions were reported in the infants. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped oral acetaminophen use and recurred when she resumed oral acetaminophen use.

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/s/

LEYLA SAHIN
02/09/2015

LYNNE P YAO
02/10/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 17, 2014
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 206610
Product Name and Strength:	Acetaminophen for Injection (b) (4)
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Agila Specialties Inc.
Submission Date:	May 3, 2014
OSE RCM #:	2014-2047
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Agila Specialties submitted this 505(b)2 NDA application for approval of Acetaminophen for Injection for the treatment of pain and reduction of fever. Thus, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) consulted DMEPA to evaluate the container labels, carton labeling, and insert labeling from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D N/A
ISMP Newsletters	E
Other	F N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the similarities and differences between the proposed product and the Reference Listed Drug (RLD), Ofirmev (NDA 022450). We determined that both products have the same route and rate of administration, strength, dose, frequency, and container/closure (100 mL glass vial) as the RLD. The dosage form of the proposed product (lyophilized powder) differs from the RLD (solution), and the 'use by' requirements also differ between products. See Appendix A for product characteristics.

We do not object to the introduction of another acetaminophen for intravenous infusion product in a glass vial to the market, despite reported cases of Ofirmev and Naropin product selection errors (see Appendix B). In these error cases, the nurse accidentally mistook a Naropin bottle sitting nearby as an Ofirmev bottle due to their similar size, shape, and cap colors. We considered the risk for product selection errors between this product and Naropin, but determined this product can be safely introduced to the market because the container labels and carton labeling are dissimilar enough that we do not anticipate product selection errors occurring. See Appendix G.3 for a side by side comparison.

Our review of the labels and labeling for this product identified additional areas of vulnerability that may be subject to confusion and can be further optimized. This includes the presentation of dose and strength in milligrams (mg), relocating the preparation instructions to a more appropriate location in the insert labeling, and general revisions to the language in Section 2.4 and Section 3. We provide recommendations to address these in Sections 4.1 below.

4 CONCLUSION & RECOMMENDATIONS

We find the addition of this product to the market acceptable. The proposed labels and labeling for this product can be improved to increase the readability and prominence of important information on the label and add important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comment

1. Errors have occurred when the use of two different units of measure to describe strength and dose has been used in the labeling. The insert labeling for this product contains both (b) (4) and 'mg' for milligrams. We recommend changing the gram expression in the insert labeling to milligrams to have one consistent unit of measure. Thus, '1 g' or '1 gm' should be revised to 1,000 mg.

B. Full Prescribing Information, Section 2.1

1. The preparation information at the beginning of Section 2.1 should be re-located to section 2.4. See Appendix G.4 for the proposed tracked changes.

C. Full Prescribing Information, Section 2.4

1. We provide recommendations in tracked changes in Appendix G.4 to optimize the language in Section 2.4.

D. Full Prescribing Information, Section 3

1. We provide recommendations in tracked changes in Appendix G.4 to optimize the language in Section 3.

4.2 RECOMMENDATIONS FOR THE AGILA SPECIALTIES

We recommend the following be implemented prior to approval of this NDA:

Container Labels and Carton Labeling

1. We recommend changing the gram expression on the container label and carton labeling to milligrams to maintain one consistent unit of measure for strength and to maintain consistency with the Reference listed Drug (RLD), Ofirmev. Thus, revise '1 g' or '1 gm' to '1,000 mg'.

Additionally, where the strength expression '1000 mg' is already used, include a comma (i.e. '1,000 mg') to minimize misinterpretation when practitioners read the strength expression.[1] Errors have occurred when the use of two different units of measure to describe strength and dose have been used in the labeling. The container label and carton labeling for this product contains both 'g' for gram and 'mg' for milligrams.

2. To help minimize the risk of overdose errors that could occur when doses less than 1,000 mg are prepared, move the statement "Doses less than 1,000 mg require aseptic transfer to a separate container prior to dispensing" to the principal display panel (PDP). Place this statement directly below the statement "For Intravenous Use Only". This important information will remind practitioners that smaller doses need to be measured and placed in a sterile empty container to prevent the whole vial from being infused, which would result in an overdose. To make room for this statement, consider removing the statements "Single-use vial" and "Lyopholized" on the PDP. This information is already located on the right side of the container label.

3. Revise the reconstitution instructions on the right side of the container label to include the strength when reconstituted. Also, bold the volume of sterile water (98 mL) required to reconstitute and the final strength expression. Lastly, place a box around this information to increase its prominence on the label. For example:

> **Preparation of Solution:**
> Inject **98 mL** of sterile water for injection, USP into the vial. Shake vial until a clear solution is achieved. After reconstitution, the vial contains **1,000 mg/100 ml (10 mg/mL)**. Use within 12 hours of reconstitution.

Container Label

1. Remove the statement [redacted] (b) (4) This information is conveyed in the insert labeling as a boxed warning statement and this is statement is not on the container labels of the Reference Listed Drug, Ofirmev.

[1] http://www.ismp.org/tools/errorproneabbreviations.pdf. Accessed November 19, 2014.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Acetaminophen for Injection that Agila Specialties submitted on May 3, 2014, and the listed drug (LD).

Table 2. Relevant Product Information for Acetaminophen and the Listed Drug

Product Name	**Acetaminophen for Injection**	**Ofirmev**
Initial Approval Date	N/A	November 2, 2010
Active Ingredient	Acetaminophen	Same as proposed product
Indication	• Management of mild to moderate pain • Management of moderate to severe pain with adjunctive opioid analgesics • Reduction of fever	Same as proposed product
Route of Administration	Intravenously via Intravenous Infusion over 15 minutes	Same as proposed product
Dosage Form	Lyopholized Powder for Injection for Intravenous Administration	Solution for Intravenous Administration
Strength	1000 mg/100 mL	1000 mg/100 mL

Table 2. Relevant Product Information for Acetaminophen and the Listed Drug		
Dose and Frequency	**Adults and Adolescents Weighing 50 kg and Over:** • 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. **Adults and Adolescents Weighing Under 50 kg:** • 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. **Children:** • Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours.	Same as proposed product
How Supplied/Container Closure	100 mL glass vial containing 1000 mg acetaminophen. One vial is packed in a carton	100 mL glass vial containing 1000 mg acetaminophen. Each carton contains 24 vials
Storage	Room temperature Use within (b)(4) hours after opening	Same as proposed product Use within (b)(4) hours after dilution

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 12, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**March 5, 2014 to October 31, 2014** **Date of last search – March 4, 2014 in OSE review# 2013-2854**
Product	**Ofirmev** [product name]
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified 7 cases, of which 4 described errors relevant for this review. All 4 cases involved wrong product selection where Naropin was infused instead of Ofirmev. Naropin is indicated for epidural use only, but was given intravenously due to the confusion with Ofirmev. In three of the 4 cases, the patient developed seizures. In each case, it was noted that the Ofirmev bottle and the Naropin bottle were a similar size and shape; thus leading to product selection error and the wrong drug to be administered.

We excluded 3 cases because they were foreign cases.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	FDA Recd Date	Narrative	MFR Ctrl #
10267970	6/26/2014	CRNA requested to administer IV Acetaminophen by patient. Bottle of IV medication punctured and attached through piggyback tubing. Patient began to experience the following symptoms: SOB, Dizziness, Visual changes, anxiety. Medication stopped immediatley. Upon examination of bottle of medication realized mistake in choice of similar appearing products. Instead of administering OFIRMEV (acetaminophen) a bottle of 0.2% Naropin (ropivicaine) had been administered. The total amount of ropivacaine given was 20 ml. Actions taken: were to change complete IV setup, monitor VS, EKG ordered. Attending MDA notified. Symptoms subsided within 5 minutes. Dr. CRNA discussed event with patient. Head of Anesthesia and Head of CRNA's notified of the event. RN notified department manager of event. (Medication/Dose ordered: Ofirmev IV; Medication/Dose given: Naropin (approx 40 mg) via IV route; Number of times error occurred: 1; Where in med process error occurred: Administration;). Naropin infusion bottle and Ofirmev infusion bottle are both glass 100 ml bottles with blue caps. The lids/caps are different shades of blue and the writing on the bottles is different. Anesthesia does not scan medications; both products ordered for the patient. Naropin infused via the incorrect route.	None

Case #	FDA Recd Date	Narrative	MFR Ctrl #
10270795	6/26/2014	RN called to L&D OR; patient was having a seizure. Upon entering room, RN noticed blood pressure of 30's/20's. RN witnessed second seizure at this time. MD stated this was the patient's second seizure. Rapid Response Team called to OR. RN drew attention to low blood pressure to Anesthesia and Dr. Rapid Response Team arrived, took over care and transferred patient to ICU. After RRT called, ICU RN in patient room (C319) for the admission of post C-section L&D patient to ICU post seizures x 2. RN found empty bottle of Ropivacaine hanging IV piggyback with Lactated Ringers. Anesthiologist in room. Dr. immediately notified. (Medication/Dose ordered: Ofirmev 1 gm/100 ml IV; Medication/Dose given: Ropivacaine 0.2% 200 mg/100 ml IV; Number of times error occurred: 1; Where in med process error occurred: Administration;) Naropin infusion bottle and Ofirmev infusion bottles are both glass 100 ml bottles with blue caps. The lids/caps are different shades of blue and the writing on the bottles is different. Anesthesia does not scan medications; both products ordered for the patient. Naropin infused via the incorrect route.	None

Case #	FDA Recd Date	Narrative	MFR Ctrl #
10406976	8/25/2014	This report was received 18AUG2014 via a lay press newsletter received by a company representative and has not been medically confirmed. The Institute for Safe Medication Practices (ISMP) released a newsletter dated 14AUG2014 that contained a report of a patient receiving an infusion of Naropin (ropivacaine) instead of Ofirmev (acetaminophen). The ISMP report read as follows: "An elderly surgical patient in a post-anesthesia care unit was prescribed a dose of IV acetaminophen (OFIRMEV). The patient's nurse picked up what she thought was an infusion bottle of acetaminophen from a nearby table and began to infuse it. After just 10 minutes, the patient experienced tonic-clonic seizures. It turned out that someone had placed an infusion bottle of ropivacaine (NAROPIN) near the acetaminophen, and the nurse picked up the wrong container. Emergency steps were immediately carried out, including lipid infusion, and the patient recovered. The local anesthetic ropivacaine is used for epidural infusion when a prolonged anesthetic block is needed. It is also used for peripheral nerve blocks but never given IV, which can lead to cardiac arrhythmia or arrest." The ISMP report also stated "This is the fourth report we have received about this potentially fatal mix-up in which a glass bottle of Naropin was mistaken for Ofirmev". The patient recovered from the seizures. The outcome of the other events was not reported and no further information will be available.	US-MALLINCKRODT-T201403190

Case #	FDA Recd Date	Narrative	MFR Ctrl #
10452194	9/12/2014	Description: A 79 YO recovering in PACU was to receive ropivacaine via the PNC (peripheral nerve catheter). RN grabbed the bottle from the table surface that was left for her and thought that it was acetaminophen IV (Ofirmev). The RN then connected the ropivacaine 100ml vial with IV tubing believing that she was administering acetminophen. The drug was infusing at -400ml/hr and after -10min, the Pt exhibited tonic clonic seizures. Emergency steps were immediately carried out, including infusion of lipids, and Pt recovered. Medication administered to or used by the patient: Yes Outcome: Pt exhibited tonic clonic seizures. Emergency steps were immediately carried out, including infusion of lipids, and Pt recovered.	None

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on November 12, 2014 using the terms, Acetaminophen, APAP, and Ofirmev to identify reviews previously performed by DMEPA.

C.2 Results

We have performed five label and labeling reviews and one post market medication error review for Ofirmev (NDA 022450).[2,3,4,5,6,7] Three of the label and labeling reviews were conducted prior to initial approval of Ofirmev.

The most recent Ofirmev label and labeling (OSE review (b) (4) under NDA 022450) provided recommendations for (b) (4) the currently marketed vial for intravenous infusion. In the post market medication error review, OSE Review 2012-1016 dated August 8, 2012, under NDA 022450, we summarized 29 post-marketing reports of pediatric and adult wrong dose medication errors involving Ofirmev and its foreign counterpart, Perfalgan for the Pediatric Advisory meeting held September 2012.[8] OSE review# 2013-329 under NDA 022450 provided recommendations to address the findings of the post market medication error review, including changes to the insert labeling to help reduce the risk of dosing errors in pediatrics and adults. All previous label and labeling recommendations have been implemented for the Ofirmev vial labels and labeling.

We conducted a FAERS search for Ofirmev medication errors in OSE review # 2012-2519 to inform recommendations for the labels and labeling for Acetaminophen Injection (NDA 204767). The FAERS search did not retrieve any medication error cases. However, the Office of Surveillance and Epidemiology approved a post-market waiver for Cadence Pharmaceuticals to

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[2] OSE review # 2009-1010. Label and Labeling Review for Acetaminophen Injection 1000 mg/100 mL vial. Abate, R. October 6, 2009.

[3] OSE Review # 2009-2204. Label and Labeling Review for Ofirmev (Acetaminophen) Injection 1000 mg/100 mL vial. Abate, R. December 17, 2009.

[4] OSE Review # 2010-1118. Label and Labeling Review for Ofirmev (Acetaminophen) Injection 1000 mg/100 mL vial. Abate, R. September 13, 2010.

[5] OSE Review # 2012-1016. Post-marketing Medication Error Review for Acetaminophen Injection. Baugh, D. August 8, 2012.

[6] OSE Review # 2013-329. Label and Labeling Memorandum for Ofirmev (Acetaminophen Injection). Baugh, D. March 15, 2013.

[7] OSE Review #2013-2854. Label and Labeling Review for Ofirmev (Acetaminophen) Injection 1000 mg/100 mL infusion bag.

[8] Advisory Committees: 2012 Meeting Materials, Pediatric Advisory Committee to the Food and Drug Administration [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; [updated 2013 Feb]. Available from: http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm283814 htm

submit Ofirmev non-serious expected events to the FDA, so there may be medication error cases that have not been submitted to the FDA or entered into the FAERS database.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on November 12, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: Ofirmev and newsletters published after March 1, 2014

E.2 Results

We identified 2 articles[9,10] that involved product selection confusion between Ofirmev and Naropin. It is unclear in the July 3, 2014 article if the reported cases were duplicate cases in our current FAERS search (See Appendix B). The August 14, 2014 article was a duplicate of FAERS case# 10452194 (see Appendix B.3 for more details). The root cause in both articles was attributed to the similar shape and size of the glass bottle for both products. Additionally, each product is a sterile colorless solution that is packaged in a ready to use format, increasing the chances for confusion. Lastly, the articles discussed the increased risk of selection error when the similar looking products were also stored near each other.

[9] ISMP Acute Care Newsletter. Safety Briefs, Confusion Between Naropin for Epidural Infusion and Ofirmev IV. Vol 19, Issue 13. July 3, 2014. Pg.1

[10] ISMP Acute Care Newsletter. Worth Repeating: Another Dangerous Ofirmev-Naropin Mix-up. Vol 19, Issue 16. August 14, 2014. Pg. 1

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[11] along with postmarket medication error data, we reviewed the following Acetaminophen for injection labels and labeling submitted by Agila Specialties on May 3, 2014 and August 7, 2014.

- Container label (May 3, 2014)
- Carton labeling (May 3, 2014)
- Working Draft of Prescribing Information as of December 17, 2014

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[11] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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12/17/2014

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12/17/2014